Sorafenib Tosylate

Cat. No.: HY-10201A

CAS No.: 475207-59-1

Molecular Formula: $C_{28}H_{24}ClF_3N_4O_6S$

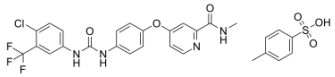
Molecular Weight: 637.03

Target: Raf; VEGFR; FLT3; Autophagy; Ferroptosis; Apoptosis

Pathway: MAPK/ERK Pathway; Protein Tyrosine Kinase/RTK; Autophagy; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 31 mg/mL (48.66 mM)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.5698 mL	7.8489 mL	15.6978 mL
5 mM	0.3140 mL	1.5698 mL	3.1396 mL
10 mM	0.1570 mL	0.7849 mL	1.5698 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2.08 mg/mL (3.27 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (3.27 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.27 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Sorafenib Tosylate (Bay 43-9006 Tosylate) is a potent and orally active Raf inhibitor with IC_{50}s of 6 nM and 20 nM for Raf-1 and B-Raf, respectively. SorafenibTosylate is a multikinase inhibitor with IC_{50}s of 90 nM, 15 nM, 20 nM, 57 nM and 58 nM for VEGFR2, VEGFR3, PDGFRβ, FLT3 and c-Kit, respectively. Sorafenib Tosylate induces autophagy and apoptosis. Sorafenib Tosylate has anti-tumor activity. Sorafenib Tosylate is a ferroptosis activator[1].

IC_{50} & Target				
	VEGFR3 20 nM (IC_{50})	Braf 22 nM (IC_{50})	Raf-1 6 nM (IC_{50})	VEGFR2 90 nM (IC_{50})
	$Braf^{V599E}$ 38 nM (IC_{50})	PDGFRβ 57 nM (IC_{50})	c-Kit 68 nM (IC_{50})	Flt3 58 nM (IC_{50})

In Vitro

Sorafenib Tosylate also inhibits $BRAF^{wt}$ (IC_{50}=22 nM), $BRAF^{V599E}$ (IC_{50}=38 nM), VEGFR-2 (IC_{50}=90 nM), VEGFR-3 (IC_{50}=20 nM), PDGFR-β (IC_{50}=57 nM), c-KIT (IC_{50}=68 nM), and Flt3 (IC_{50}=58 nM) in biochemical assays[1]. Sorafenib-induced phosphorylation of c-Met, p70S6K and 4EBP1 is significantly reduced when 10-0505 cells are co-treated with anti-human anti-HGF antibody, suggesting that treatment with Sorafenib Tosylate leads to increased HGF secretion and activation of c-Met and mTOR targets[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Sorafenib Tosylate (10, 30, 50 and 100 mg/kg, orally) treatment inhibits the tumor growth of 06-0606 and 10-0505 xenografts in a dose-dependent manner (P<0.01). The growth rate of 06-0606 and 10-0505 xenografts is also significantly reduced by Sorafenib. The weights of 06-0606 tumors in mice that are treated with Sorafenib 50 mg/kg and 100 mg/kg are approximately 13% and 5% of the controls, respectively. 50 mg dose of Sorafenib significantly inhibits tumor growth in mice with lines 5-1318, 26-1004 and 10-0505 (P<0.01). For 50 mg dose, the T/C ratio, where T and C are the median weight (mg) of Sorafenib- and vehicle-treated tumors at the end of the treatment, respectively, for 06-0606, 26-1004, 5-1318, and 10-0505 xenografts is 0.13, 0.10, 0.12 and 0.49, respectively[2]. The survival rate is 73.3 % in Diethyl nitrosamine (DENA) group and 83.3 % in Sorafenib group compared to 100 % in the normal control group. DENA group shows a significant increase in liver index (1.51-fold increase, p<0.05) compared to normal control group, while treatment with Sorafenib shows significant decrease (p<0.05) in liver index when compared to DENA group. The liver index in Sorafenib group significantly decreases to lower than its value in the normal control[3].

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PROTOCOL

Kinase Assay [1]

To test compound inhibition against various RAF kinase isoforms, Sorafenib is added to a mixture of Raf-1 (80 ng), wt BRAF, or V599E BRAF (80 ng) with MEK-1 (1 μg) in assay buffer [20 mM Tris (pH 8.2), 100 mM NaCl, 5 mM $MgCl_2$, and 0.15% β-mercaptoethanol] at a final concentration of 1% DMSO. The RAF kinase assay (final volume of 50 μL) is initiated by adding 25 μL of 10 μM γ-[^{33}P]ATP (400 Ci/mol) and incubated at 32°C for 25 minutes. Phosphorylated MEK-1 is harvested by filtration onto a phosphocellulose mat, and 1% phosphoric acid is used to wash away unbound radioactivity. After drying by microwave heating, a β-plate counter is used to quantify filter-bound radioactivity[1].

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Cell Assay [2]

The 10-0505, 06-0606, and 26-1004 tumors are finely minced and washed three times with modified Eagle medium (MEM). Cells are harvested by centrifuging at 800× g for 10 min. Cells are treated with 3 or 6 μM of Sorafenib in serum free MEM in the presence or absence of 5 μg/mL anti-human hepatocyte growth factor (HGF) antibody for 48 hrs. A total of 2 mL of conditioned medium from vehicle- or Sorafenib-treated (without anti-human antibody) is collected and concentrated using a VIVASPIN 20 and secreted HGF in conditioned medium is determined by western blotting[2].

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Animal Administration [2][3]

Mice[2]

For dose-response experiment, mice bearing the 06-0606 and 10-0505 xenografts are given four doses of Sorafenib (10, 30, 50 and 100 mg/kg daily) orally for 12 days. Each treatment group comprised of five mice. To investigate the antitumor effects of Sorafenib, mice bearing tumors are orally administered 50 mg/kg Sorafenib daily for 12 days. Each treatment group is comprised of 14 animals and each experiment is repeated at least twice. Treatment started on day 7 after tumor implantation. By this time, the HCC xenografts reached the size of approximately 100 mm^3. To study the effects of Rapamycin plus Sorafenib on the growth of 10-0505 xenograft, mice bearing tumors (14 per group) are orally administered either 200 μL of vehicle, or 50 mg/kg of Sorafenib, or 1 mg/kg of Rapamycin, or Rapamycin plus Sorafenib daily for indicated days. Tumor growth is monitored at least twice weekly by Vernier caliper measurement of the length and width of tumor.

Tumor volume is calculated as follows: [length×width^2×π/6]. At the end of the study, the mice are killed with body and tumor weights being recorded, and the tumors harvested for analysis.

Rats[3]

In the study, 100- to 120-g male albino rats are utilized. After acclimatization period, rats are weighed and randomly divided into three groups: Group 1 (normal control group; n=10) is given the vehicle daily for 8 weeks. Group 2 (DENA group; n=15) receive i.p. single dose of 200 mg/kg DENA. Group 3 (Sorafenib group; n=12) is given Sorafenib orally at a dose of 10 mg/kg daily for 2 weeks, 6 weeks after DENA i.p. injection. At the end of the experiment (8 weeks), rats are weighed, anesthetized by ether, and killed, and their livers are dissected. Fresh liver is washed twice with ice-cold saline, dried on clean paper towel, and weighed. Liver index is calculated as liver weight (g)/final body weight (g)×100. The liver is divided into five portions: one portion is preserved in 10 % formalin for histopathological examination and the other portions are immediately frozen in liquid nitrogen and stored at −80°C.

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CUSTOMER VALIDATION

- Cancer Discov. 2019 Dec;9(12):1686-1695.
- Sci Transl Med. 2018 Jul 18;10(450). pii: eaaq1093.
- ACS Appl Mater Interfaces. 2017 Apr 12;9(14):12195-12202.
- Theranostics. 2020 Aug 21;10(23):10498-10512.
- Br J Pharmacol. 2020 Nov 3.

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REFERENCES

[1]. Wilhelm SM, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004 Oct 1;64(19):7099-109.

[2]. Huynh H, et al. Sorafenib and rapamycin induce growth suppression in mouse models of hepatocellular carcinoma. J Cell Mol Med. 2009 Aug;13(8B):2673-83.

[3]. El-Ashmawy NE, et al. Sorafenib effect on liver neoplastic changes in rats: more than a kinase inhibitor. Clin Exp Med. 2016 Apr 16.

[4]. Zhu W, et al. Combination of sorafenib and Valproic acid synergistically induces cell apoptosis and inhibits hepatocellular carcinoma growth via down-regulating Notch3 and pAkt. Am J Cancer Res. 2017 Dec 1;7(12):2503-2514.

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